Validation of current practice and a near patient testing method for oral-anticoagulant control in general practice

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SUMMARY

When oral anticoagulant control is monitored in general practice, venous blood samples are usually transported to a central laboratory for determination of international normalized ratio (INR). An alternative is near patient testing by a commercial method.

In a rural general practice 27 km from a central haematology laboratory, whole blood samples were drawn from patients receiving oral anticoagulants and analysed by three methods: after centrifugation, plasma separated and frozen in liquid nitrogen, transported to the laboratory, thawed and immediately analysed (control); courier transport of citrated sample to the laboratory for analysis (routine); near patient testing of whole blood sample (NPT). Maximum temperature achieved and time to analysis for routine samples were recorded.

306 complete sets of data were obtained. Comparison between the routine method and the control method revealed acceptable agreement. On multiple regression analysis, maximum temperature achieved did not contribute to differences observed but time to analysis of over 5 hours did make a significant contribution. Comparison between the NPT method and control method showed acceptable agreement, with persistent under-recording by the NPT method.

The routine method for INR determination was validated as robust and reproducible with the proviso that needle-to-analysis time should be kept below 5 hours. The NPT method was valid under conditions of normal general practice. Strict quality control of NPT methods is essential if performance is to be comparable with that of established methods.

INTRODUCTION

With advances such as near patient testing (NPT) and computerized decision support, monitoring of oral anti-coagulation in British primary care has become more feasible[1]. Preliminary results of a randomized controlled trial comparing NPT in primary care with conventional management have been published[2]. Reasons for adopting NPT methods include rapid availability of results and convenience for patients and clinicians. However, a NPT method needs to be reliable, precise and the equal of the method it replaces. Results that appeared spurious led general practitioners in the Honiton Practice to question the reliability of the current system of transportation and analysis of blood samples taken in the surgery for determination of international normalized ratio (INR). The aims of this study were to examine the effect on INR measurements of transportation of blood samples from a rural general practice to a central laboratory and in parallel examine the validity of a commercially available NPT method (Boehringer Mannheim Coaguchek Coagulation Monitor).

METHOD

The Honiton Group practice has a list size of 14 500 with about 120 patients having their anticoagulation monitored at any one time. Around 1000 blood samples are taken each year for INR determination by the practice phlebotomist. The samples are taken into citrate tubes, packed into plastic transport boxes and collected once a day at 1 pm by the health authority courier. Samples are taken to the haematology laboratory in Exeter (27 km away) for analysis on the same day. Analysis in Exeter is performed on an Instrumentation Laboratory Futura analyser using rabbit thromboplastin (IL Combined PT FIB-HS PLUS) and is subject to in-house and national quality control schemes.

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The international sensitivity index of the laboratory analyser thromboplastin is determined by the UK National External Quality Control Scheme (NEQAS). During the months of June–September inclusive blood samples were taken with the Sarsted Monovet system. The first sample was drawn with an adapter and 1 mL plastic syringe. This whole blood sample was analysed immediately on a near patient Coaguchek machine (NPT sample). The nurse phlebotomist received training in use of the NPT method from the company representative and the local haematology staff. The NPT method was run in parallel for two weeks before the study began. The Coaguchek system involves placing a drop of venous or capillary blood onto a test strip coated with iron oxide particles and rabbit brain thromboplastin. The iron oxide particles are subjected to regular magnetic field changes. As a fibrin matrix is formed the movement of iron oxide particles finally stops and a reduction in reflectance is recognized by the instrument as the onset of coagulation. The batch international sensitivity index of the Coaguchek is integrated into the system by insertion of a test strip specific to each batch of reagent strips. The use of venous whole blood rather than capillary whole blood has been validated previously (Boehringer Mannheim, unpublished), and we did not wish to subject patients to finger-pricking as well as venepuncture. It was also relevant that the NEQAS samples consisted of lyophilized plasma samples derived from venous blood. The second and third samples were drawn into standard citrate tubes. The second sample was packaged and transported as normal (routine sample); the third sample was immediately centrifuged at 3000 rpm for 10 minutes, plasma then being separated and frozen in liquid nitrogen (control sample). The frozen samples were taken separately to Exeter and thawed in a water bath held at 37 °C. These samples were then analysed in one batch on the Futura analyser.

Time taken from sampling to analysis for routine samples was recorded. A maximum–minimum thermometer was placed in the transport box each day and the maximum ambient temperature achieved was recorded.

INR values for samples processed by the three methods were entered into a spreadsheet along with time to analysis and maximum temperature reached for the routine samples. The data were analysed with the SPSS package and the method described by Bland and Altman[3], which is used increasingly to assess agreement between two sets of measurements. In this study the difference in INR between two methods was plotted against the average INR from the two methods. If 95% of the results fell within plus or minus two standard deviations from the mean then agreement was considered satisfactory. Intra-assay variation for each method was assessed. Liquid nitrogen transportation was validated by analysing ten identical samples of blood with differing INR values from four patients straightaway on the Futura machine and comparing the results with identical samples separated, frozen in liquid nitrogen for 4 hours, thawed in a water bath at 37 °C and analysed on the Futura machine. The NPT method was subject to in-house quality control and UK NEQAS monitoring.

RESULTS

Complete sets of data were obtained on 306 blood samples. The time to analysis ranged from 4 to 7 hours. Maximum temperatures achieved ranged from 22 to 40 °C. No significant differences were observed between the INR values from 4 patients determined on duplicate samples analysed ten times before and after freezing in liquid nitrogen (paired t-test), thus validating the control method. The ten identical samples analysed by the Futura method had a coefficient of variation of 2–4% (mean INR values of the 4 patients 1.7, 1.9, 2.9, 3.5).

Analysis of ten identical samples from 2 patients with the NPT method produced a coefficient of variation of 8% (mean INR 1.1) and 12% (mean INR 2.4). The NPT method was subjected on three occasions to testing under the NEQAS and on each occasion results fell within the accepted range.

Correlation between the routine method and the control method was high (Pearson r=0.945, P<0.0001). Figure 1 illustrates the comparison between the routine method and the control method, the difference in INR being plotted against the average INR from the two methods. The mean difference of routine results from the control results was −0.08 INR units, 2 standard deviations from the mean being +0.47 and −0.63 INR units. 95% of the results fell within 2 SD of the mean.

Correlation between the NPT method and the control method was high (Pearson r=0.850, P<0.0001). Figure 2 illustrates the comparison between the NPT method and the control method. The mean difference of NPT results from the control results was −0.32 INR units, 2 SD from the mean being +0.55 and −1.20 INR units. 95% of the results fell within 2 SD of the mean.

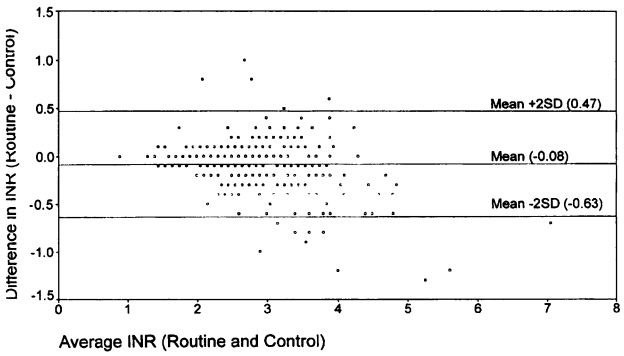

Figure 1 **Difference against mean for control and routine international normalized ratio (INR) values**

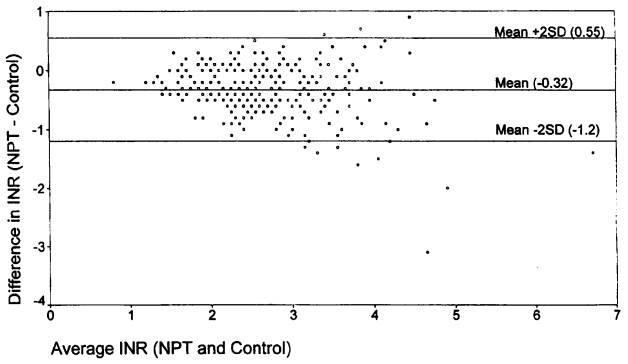

Figure 2. **Difference against mean for control and near-patient testing method (NPT) international normalized ratio (INR) values**

Multiple regression analysis for the routine method samples showed that the maximum temperature reached during transit made no significant contribution to the differences observed. However, the time to analysis did explain some of the variation. For samples analysed in under 5 hours, the time to analysis did not contribute significantly to differences observed, but for samples analysed 5 hours or more after collection (less than 5% of the total number of samples) the time to analysis contributed significantly.

DISCUSSION

The first aim of this study was to validate the current practice of venous blood sampling in primary care and transportation to a central haematology laboratory for INR determination. In a recent study Baglin and Luddington[4] found no significant change in INR in blood samples stored for up to three days. However, this was a laboratory based study and did not take into account temperature change and other possible transportation effects on samples taken from primary care settings distant from a haematology laboratory. In our study liquid nitrogen storage and thawing had no significant effect on the INR value, so the liquid nitrogen transported samples could reasonably be considered as controls. The Bland and Altman analysis of routine samples compared with control samples indicated that the mean difference between the two groups was small enough to be clinically insignificant (−0.08 INR unit) and that 95% of the routine sample results fell within 2 SD of the mean difference between the two methods. The limits of agreement (−0.63 and 0.47) are small enough for confidence that the routine method produces clinically acceptable results. Temperature had no important effect, and time to analysis only contributed significantly to differences observed when greater than 5 hours. It is reassuring that the routine method fulfilled the current guidelines of the British Standards Institution for repeatability[5].

There has been increasing commercial pressure to consider near patient testing in primary care and Hobbs *et al.*[6] have reviewed the relevant publications. Their report indicates a need for validation of the performance of NPT methods in routine clinical settings. The second aim of our study accords with this need. The analysis of the NPT samples compared with the control samples indicated a persistent under-reading of the INR results (mean difference −0.32 INR units)—also remarked upon in the Medical Devices Agency (MDA) evaluation of this method[7]. Of the NPT results 95% fell within 2 SD of the mean difference between the two methods with somewhat wider limits of agreement (−1.20 and +0.55 INR units), an observation very close to that of the MDA evaluation[7]. The NPT method performed acceptably in terms of imprecision and in the external quality control scheme. We did not assess the patient acceptability of NPT and finger-prick testing. However, others have found capillary blood testing acceptable[8].

This study has found the routine method for INR determination in this health authority robust and reproducible. We also obtained reassuring evidence that, under routine conditions in a busy primary care setting, the NPT method performed within acceptable limits. The persistent under-recording by the Coaguchek system presumably relates to the variations observed in thromboplastins and the lack of a true gold standard for INR measurement. Most manufacturers of NPT equipment for haematology tests persist in providing comparative evaluations based on correlation coefficients—a tendency discussed critically by Bland and Altman[3]. It is crucial that before NPT methods are adopted they should be rigorously field tested in relevant settings. In addition NPT methods should be subject to strict internal and external quality control if performance is to remain comparable with that of more sophisticated centralized services[9].

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